ORIGINAL ARTICLE

Invasive pneumococcal infections: a clinical and microbiological analysis of 53 patients in Taiwan

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Objective To track penicillin susceptibility among *Streptococcus pneumoniae* causing invasive diseases and to evaluate risk factors for antibiotic resistance.

Methods A retrospective study was performed in a medical center of all patients with invasive pneumococcal infections based on positive microbiological findings, confirmed by appropriate clinical and laboratory findings. MICs of penicillin and ceftriaxone were determined and interpreted by NCCLS methodology.

Results Fifty-three episodes of invasive *S. pneumoniae* infections (ISPI) among 22 children and 31 adults were identified. The disease patterns of ISPI were similar between children and adults, and the most common modes were pneumonia (70%) and primary bacteremia (23%). The rate of penicillin-nonsusceptible *S. pneumoniae* (PNSP) isolated from pediatric patients was higher than that in adult patients (95.5% vs. 54.8%, $P < 0.001$). This finding was correlated to prior antibiotic use that was more common in children (36.4%) than in adults (18.9%). The rate of penicillin-resistance among *S. pneumoniae* isolates (PRSP) was extremely high in this area: 45.5% from pediatric patients and 41.9% from adult patients. More adults (90.3%) with ISPI had major underlying diseases than children (4.5%). This may explain why adult patients tended to run an unfavorable outcome (mortality rate, 51.6% and 4.5% in adults and children, respectively), although most of the cases with empyema were children. None of the patients enrolled in this study received pneumococcal vaccination.

Conclusion We suggest that vaccines be administered for young children and the elderly with major underlying diseases to prevent ISPI.

Keywords *Streptococcus pneumoniae*, invasive infection, penicillin resistance

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INTRODUCTION

Over the past few years, isolates of *Streptococcus pneumoniae* that are resistant to antibiotics have been recovered with increasing frequency from patients with both systemic infections and infections of the upper respiratory tract [1]. Similarly, nasopharyngeal colonization by antibiotic-resistant *S. pneumoniae* is steadily escalating [2,3]. In general, pneumococcal isolates recovered from younger children or from upper respiratory sites are more likely to be resistant to antibiotics than are isolates recovered from older children or adults, or those recovered from normally sterile sites [4,5]. Furthermore, previous antibiotic use, underlying illness, recent hospitalization, and day-care attendance have been associated with antibiotic-resistant *S. pneumoniae* in many studies [5,6].

The treatment of patients with pneumococcal infection has been complicated by the development of antibiotic resistance [7]. The lack of clinical

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data of invasive pneumococcal infections creates difficulty in determining the best antibiotic treatment for such patients. This report describes systemic pneumococcal infections in children and adults treated in a medical center during a 1-year period. The intent of this study was to track antibiotic susceptibility for penicillin among *S. pneumoniae*-causing systemic infections and to evaluate risk factors for antibiotic resistance.

MATERIALS AND METHODS

All patients admitted and treated in Chang Gung Memorial Hospital and Children's Hospital between April 1, 2000 and March 31, 2001 with invasive infections (meningitis, bacteremia, pneumonia, septic arthritis, cellulites, peritonitis, and so forth) attributable to *S. pneumoniae* were included in this study. Patients were identified by reviewing the results of our hospital's microbiology laboratory. Invasive infections had to be documented by a positive culture from a normally sterile site, i.e. a diagnosis of pneumococcal pneumonia required a positive culture of blood or pleural fluid. Isolates were identified as *S. pneumoniae* by standard laboratory techniques. A standardized data form including demographic and clinical information was completed retrospectively for each episode of pneumococcal infection. Pneumococcal meningitis was defined as either a cerebrospinal fluid (CSF) culture that was positive for *S. pneumoniae* or a CSF pleocytosis (>5 white blood cells/mm^3) plus a blood culture positive for *S. pneumoniae.* Pneumococcal pneumonia required a chest radiograph consistent with pneumonia in addition to the positive culture. MIC determinations for penicillin and ceftriaxone were performed by standard microbroth dilution with Mueller-Hinton media supplemented with 3% lyzed horse blood [8]. Susceptibility categories were determined by the 1997 National Committee for Clinical Laboratory Standards (NCCLS) guidelines for breakpoints (penicillin: $\leq$0.06 mg/L = susceptible; 0.1–1.0 mg/L = intermediate; $\geq$2.0 mg/L = resistant; ceftriaxone: $\leq$0.5 mg/L = susceptible; 1.0 mg/L = intermediate; $\geq$2.0 mg/L = resistant) [8]. Isolates in the intermediate or resistant categories were considered non-susceptible.

On the other hand, the following clinical data of the patients were collected and analyzed: demographic data, underlying diseases, symptoms, vital signs on admission, laboratory data, cerebrospinal fluid data in the presence of meningitis, and outcome.

RESULTS

A total of 53 episodes of invasive *S. pneumoniae* infections (ISPI) were identified in 53 patients, including 22 children and 31 adults. Fifty-eight isolates were obtained from the 53 patients: 45 from blood, seven pleural effusion, three CSF, and three sputum. The clinical characteristics of these patients are summarized in Table 1. The age range of the 22 pediatric patients was between three months and six years (mean, 3.14 years) and that of the 31 adults was between 23 and 88 years (mean, 57.13 years). The ratio of male to female appeared higher in adult patients (2.4) than in pediatric patients (1.2), while the difference was not statistically significant ($P = 0.219$). As to the symptoms, more adult patients presented with altered consciousness (45.2%) and shock (33.3%) initially ($P = 0.015$ and 0.016, respectively). The rate of previous exposure to antibiotics was significantly higher in pediatric patients than in adult patients (36.4% vs. 6.5%, $P = 0.020$). More than 90% of adult patients had major underlying diseases; in contrast, only 4.5% of pediatric patients had underling diseases ($P < 0.001$). The detail of major underlying diseases is listed in Table 2. The most common underlying diseases in adult patients were malignancy and chronic liver disease. Neither pediatric nor adult patients had history of pneumococcal vaccination prior to the disease onset. The mean duration required for a defervescence after appropriate antibiotic treatment was longer in pediatric patients than in adults (8.48 days vs. 3.88 days, $P = 0.005$). The antimicrobial susceptibility patterns of *S. pneumoniae* isolates were different between pediatric and adult patients ($P < 0.001$). Only 4.5% of pediatric isolates were penicillin-susceptible (PSSP), 45.5% penicillin-resistant (PRSP), and the remaining 50% penicillin-intermediate resistant (PISP). In contrast, 45.2% of isolates recovered from adult patients were PSSP, 12.9% PISP, and 41.9% PRSP ($P < 0.001$).

Majority of ISPI was pneumonia (69.8%) and primary bacteremia. Six pediatric patients (40%) had pneumonia complicated with empyema, while only 4.5% of adult patients with pneumonia had this complication ($P = 0.004$). Sixteen adult patients (51.6%) died eventually and 11 (35.5%)

Table 1 Comparison of clinical characteristics among children and adults with invasive *Streptococcus pneumoniae* infections

Characteristic	Children $n = 22$	Adults $n = 31$	Total $n = 53$	*P* value
Mean age (year)*	3.14 ± 1.63 (0.25–6.0)	57.13 ± 18.95 (23–88)	34.72 ± 30.50 (0.25–88)	
Sex (M/F)	12/10	22/9	34/19	0.219
Initial symptoms				
Fever	18 (81.8%)	21 (67.7%)	39 (73.6%)	0.252
Altered consciousness	3 (13.6%)	14 (45.2%)	17 (32.1%)	0.015
Shock	2 (9%)	12 (33.3%)	14 (26.4%)	0.016
Respiratory failure	4 (18.2%)	12 (33.3%)	16 (30.2%)	0.109
Previous use of antibiotics	8 (36.4%)	2 (6.5%)	10 (18.9%)	0.020
Underlying diseases	1 (4.5%)	28 (90.3%)	29 (54.7%)	<0.001
Vaccination	0	0	0	
WBC*	14259.1 ± 11489.7 (800–49700)	10819.4 ± 10586.5 (100–41800)		0.266
Defervescence*	8.48 ± 6.05 (1–21)	3.88 ± 3.22 (0–13)		0.005
Source of isolate				0.123
Blood only	14	26	40	
Blood + sputum	1	2	3	
Blood + pleural	1	0	1	
Blood + CSF	0	1	1	
CSF only	1	1	2	
Pleural only	5	1	6	
PCN usceptibility				<0.001
PSSP	1 (4.5%)	14 (45.2%)	15 (28.3%)	
PISP	11 (50%)	4 (12.9%)	15 (28.3%)	
PRSP	10 (45.5%)	13 (41.9%)	23 (43.4%)	

*Mean ± SD (range)

Table 2 Major underlying diseases in the patients with ISPI

Underlying disease	Children $n = 22$	Adults $n = 31$
Chronic liver disease	0	7
Malignancy	0	11
DM	0	5
Chronic renal disease	0	5
Under immunosuppressive therapy	0	5
Aplastic anemia post BMT	0	1
Cardiovascular disease	1	2
COPD	0	1
Total*	1	28

*$P < 0.001$

deaths considered to be related to ISPI; in contrast, only one child (4.5%) died of ISPI ($P < 0.001$). Almost all pediatric patients recovered from diseases completely. Among the patient fatalities, most (10 in 12) expired within three days after admission.

In those cases diagnosed with pneumonia, the median age was relatively younger in the group of PISP infections (62 years in PSSP, 5 years in PISP, and 50 years in PRSP). Previous antibiotic use was found in 50% of patients infected with PISP, which was higher than the rates in the other two groups ($P = 0.040$). As to radiological findings, multilobar involvement was more common in patients with PNSP infections (20% in PSSP, 29% in PISP, and 46% in PRSP), but such a difference was not statistically significant ($P = 0.384$). The rate of complications, such as empyema and respiratory failure requiring mechanical ventilation, did not differ among groups of different penicillin susceptibilities. The duration of fever after adequate antibiotic administration was not significantly different between patients in PNSP and PSSP groups (8.7 days ± 6.1 days vs. 4.7 days ± 4.4 days, $P = 0.124$).

A total of 12 cases were diagnosed with primary bacteremia, and most of them (83.3%) were infected with PRSP strains. Only three patients had meningitis, including two adults (33 and 66 years, respectively) and one infant (eight months). Among them, one adult patient had diabetes mellitus and died of progressive disease. Another adult patient who had no underlying diseases recovered well without any neurological sequelae. An infant with meningitis recovered

with oculomotor palsy. The isolates recovered from adult patients were PSSP strains, and the one from the infant was PISP.

DISCUSSION

The mean age of pediatric and adult patients with ISPI were 3.1 and 57.1 years, respectively. This was consistent with the previous reports [1–6,9–13], which showed that young children and the elderly had a higher incidence of pneumococcal infections. The initial symptoms differed between adults and children. More adult patients had altered consciousness than pediatric patients. Overall, septic shock occurred in 26.4% of patients, that is higher than the previously reported (10%) by Rahav et al. [9], but similar to that by Wu et al. (25.4%) [13] from northern Taiwan. More adult patients presented with septic shock than pediatric patients. All of the patients who presented with shock had major underlying diseases except one child aged six years who was otherwise healthy. More than 90% of adult patients had underlying diseases, while only one child (4.5%) had a debilitating condition (complex congenital heart disease). The most common underlying disease associated with ISPI was malignancy. This result was similar to Hsueh's report [14], in which malignancy also ranked the first among major underlying diseases. No HIV-infected host was found in this study.

The duration of fever after appropriate antibiotic treatment was longer in pediatric patients than adult patients. More frequent occurrence of empyema in children with pneumococcal pneumonia may be a factor contributing to a longer period of fever in pediatric patients. In the study, empyema occurred in 18.9% of overall patients. The rate, which is even higher in pediatric patients (40%), was also higher than that reported in the literature (2.5–7%) [10,14].

The disease patterns of ISPI were similar between adults and children. The most common were pneumonia (70%), primary bacteremia (23%), and meningitis (6%). The order of frequency was the same as that from previous reports [10]. The strains isolated from adults and children with ISPI were significantly different with respect to penicillin susceptibility. Overall, 28.3% of the isolates were PSSP and the remaining PNSP (28.3% intermediate and 43.4% resistant). In the pediatric patients, most of the isolates (95.5%) were PNSP, including 50% intermediate and 45.5% resistant strains. However, in adult patients, the PISP accounted for merely 12.9% and the PRSP 41.9%. This finding was correlated to the history of previous antibiotic use. Thirty-six percent of pediatric patients reported a history of previous antibiotic use before onset of disease, compared with only 6.5% of adult patients. The percentage of PNSP among total isolates was as high as the rate (76%) reported by Hsueh et al. from a multicenter surveillance study in Taiwan [15]. In contrast, only 24% and 6.8% of *S. pneumoniae* belonged to PNSP in the USA [16] and Canada [17], respectively.

The mortality rates related to ISPI remained at 15% to 43% in the literature and are higher in the elderly and in those with major underlying diseases [10]. We had similar results in this study. Several predisposing factors have been related to the PRSP infections, including young age (<four years), underlying diseases, prior antibiotic usage [18,19]. In this study, a higher percentage (46.7%) of patients infected with PISP had prior exposure to antibiotics than patients infected with PSSP (6.7%) and PRSP (8.7%). We also found that most of patients infected with PISP were children less than five years of age (data not shown). However, we failed to demonstrate the correlation between prior antibiotic use and infections with PRSP.

In conclusion, invasive pneumococcal infections are prevalent in young children and the elderly with major underlying diseases. The prevalence of PRSP (43.4%) in this area was surprisingly high. Antibiotic use should be more judicious in pediatric patients as prior antibiotic use was strongly correlated to the infections due to PISP in children. Although more pediatric patients with pneumonia developed empyema, adult patients generally had a more unfavorable outcome than children, perhaps due to the pre-existing major underlying diseases. On the basis of the results, we suggest that pneumococcal vaccines be administered for young children and the elderly with major underlying diseases to prevent ISPI.

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